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United States Patent [19]**Modak et al.**[11] **Patent Number:** **6,106,505**[45] **Date of Patent:** ***Aug. 22, 2000**[54] **TRICLOSAN-CONTAINING MEDICAL DEVICES**[75] **Inventors:** Shanta Modak, River Edge, N.J.;
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N.Y.[*] **Notice:** This patent is subject to a terminal disclaimer.[21] **Appl. No.:** 09/101,129[22] **PCT Filed:** Dec. 23, 1996[86] **PCT No.:** PCT/US96/20932

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[87] **PCT Pub. No.:** WO97/25085**PCT Pub. Date:** Jul. 17, 1997**Related U.S. Application Data**

[63] Continuation-in-part of application No. 08/583,239, Jan. 5, 1996, Pat. No. 5,772,640.

[51] **Int. Cl.⁷** A61M 5/32[52] **U.S. Cl.** 604/265; 424/422; 623/1;
428/35.1[58] **Field of Search** 604/264, 265;
424/422; 428/35.7, 36.9; 623/1[56] **References Cited****U.S. PATENT DOCUMENTS**4,605,564 8/1986 Kulla et al. .
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Primary Examiner—Mark Bockelman*Attorney, Agent, or Firm*—Baker Botts L.L.P.[57] **ABSTRACT**

The present invention relates to polymeric medical articles comprising the antiinfective agents chlorhexidine and triclosan. It is based, at least in part, on the discovery that the synergistic relationship between these compounds permits the use of relatively low levels of both agents, and on the discovery that effective antimicrobial activity may be achieved when these compounds are comprised in either hydrophilic or hydrophobic polymers. It is also based on the discovery that chlorhexidine free base and triclosan, used together, are incorporated into polymeric medical articles more efficiently. Medical articles prepared according to the invention offer the advantage of preventing or inhibiting infection while avoiding undesirably high release of antiinfective agent, for example into the bloodstream of a subject.

55 Claims, No Drawings

The amount of drug uptake per cm/catheter in catheters prepared using various soaking solutions was measured as set forth above.

TABLE XXII

Soaking Solution	Drug Uptake/cm catheter	
	Chlorhexidine	Triclosan
5% CHA	260-310[$\mu\text{g}??$]	—
5% CHA + 2% TC	280-300	450-480
2% CHX + 2% TC + 2% CHA	480-520	300-370
3% CHX + 3% TC	550-660	600-700

The luminal adherence of bacteria was quantified in catheters impregnated with antimicrobials and then coated with a solution of 2.7 percent Tecoflex 93A and various antimicrobial agents. Bacterial adherence was measured as follows. 12 cm segments of test and control 7Fr catheters were each connected to an individual channel of a peristaltic pump via an extension line, hub, and injection cap. The hubs were inoculated initially and after 24 hours with 10^6 cfu of *S. aureus* which causes the extension line to become colonized thus acting as a continuous source of bacteria for seeding lumens. The lumens were continuously perfused at a rate of 20 ml/hour with trypticase soy broth (TSB) diluted 1:10 with physiological saline over the course of 7 days. At the end of one week the catheter segments were disconnected and their outer surfaces disinfected with 70% ethanol. Each lumen was flushed with sterile TSB to remove non-adherent bacteria. Each catheter was then cut into 2 cm segment each of which is further divided into 2 mm subsegments and placed in tubes containing 4 ml of antiseptic inactivating broth (LTSB). The tubes were sonicated for 20 minutes at 4° C. to remove bacteria adhering to the lumens. To quantify the adherence, a 0.5 ml aliquot of the LTSB extract was sub-cultured on trypticase soy agar plates. The results are shown in Table XXII.

TABLE XXIII

DRUG IN SOAKING SOLUTION (cfu/cm)	DRUG IN OUTER COATING	BACTERIAL ADHERENCE IN LUMEN
5% CHA	3% CHA	3×10^4
5% CHA + 0.5% TC	2% CHA + 2% TC	3×10^2
2% CHX + 2% CHA + 2% TC	2% CHA + 2% TC	0
3% CHX + 3% TC	0.5% CHX + 0.5% TC	0
0 (Control)	0	4×10^6
2% CHX + 2% CHA + 2% TC	no outer coating	5

Various publications are cited herein, which are hereby incorporated by reference in their entireties.

What is claimed is:

1. A hydrophilic polymeric medical article which has been impregnated with a treatment solution comprising (i) between about 1 and 10 percent of a hydrophilic polymer; (ii) between 1 and 5 percent of chlorhexidine free base; and (iii) between 0.5 and 5 percent of triclosan, wherein the molar ratio of chlorhexidine free base to triclosan is between 1:1 and 1:3.

2. The medical article of claim 1 which is fabricated from a hydrophilic polymer selected from the group consisting of natural rubber latex and biomedical polyurethane.

3. The medical article of claim 1 wherein the hydrophilic polymer in the treatment solution is a biomedical polyurethane.

4. The medical article of claim 2 wherein the hydrophilic polymer in the treatment solution is a biomedical polyurethane.

5. A hydrophilic polymeric medical article impregnated with a treatment solution comprising a hydrophobic polymer, triclosan, and chlorhexidine free base, wherein the triclosan and chlorhexidine free base are present in a chlorhexidine free base:triclosan molar ratio of between 1:1 and 1:3.

6. The medical article of claim 5, further comprising silver sulfadiazine.

7. The medical article of claim 6 wherein the hydrophobic polymer is a biomedical silicone polymer.

8. The medical article of claim 6 wherein the hydrophobic polymer is a silicone-polyurethane copolymer.

9. The medical article of claim 5 wherein the hydrophobic polymer is a biomedical silicone polymer.

10. The medical article of claim 5 wherein the hydrophobic polymer is a silicone-polyurethane copolymer.

11. The medical article of claim 5 which is a catheter.

12. The catheter of claim 11 which is an intravenous catheter.

13. The catheter of claim 12 which is fabricated from a biomedical polyurethane.

14. The catheter of claim 13 wherein the hydrophobic polymer in the solution is a biomedical silicone-polyurethane copolymer.

15. A hydrophilic polymeric medical article which has been impregnated with a treatment solution comprising (i) between about 1 and 10 percent of a hydrophobic polymer; (ii) between 1 and 5 percent of chlorhexidine free base; and (iii) between 0.5 and 5 percent of triclosan, wherein the molar ratio of chlorhexidine free base to triclosan is between 1:1 and 1:3.

16. The medical article of claim 15 which is fabricated from a hydrophilic polymer selected from the group consisting of natural rubber latex and biomedical polyurethane.

17. The medical article of claim 16 wherein the hydrophobic polymer in the treatment solution is a biomedical silicone polymer.

18. The medical article of claim 16 wherein the hydrophobic polymer in the treatment solution is a silicone-polyurethane copolymer.

19. The medical article of claim 15 wherein the hydrophobic polymer in the treatment solution is a biomedical silicone polymer.

20. The medical article of claim 15 wherein the hydrophobic polymer in the treatment solution is a silicone-polyurethane copolymer.

21. A hydrophobic polymeric medical article which has been impregnated with a treatment solution comprising (i) between about 1 and 10 percent of a hydrophobic polymer; between 1 and 5 percent of chlorhexidine free base; and (iii) between 0.5 and 5 percent of triclosan, wherein the molar ratio of chlorhexidine free base to triclosan is between 1:1 and 1:3.

22. The medical article of claim 21 which is fabricated from a hydrophobic polymer selected from the group consisting of polytetrafluoroethylene, Dacron, polyvinylchloride, biomedical silicone polymer, and silicone polyurethane copolymer.

23. The medical article of claim 22 wherein the hydrophobic polymer in the treatment solution is a biomedical silicone polymer.

24. The medical article of claim 22 wherein the hydrophobic polymer in the treatment solution is a silicone-polyurethane copolymer.

25. The medical article of claim 21 wherein the hydrophobic polymer in the treatment solution is a biomedical silicone polymer.

26. The medical article of claim 21 wherein the hydrophobic polymer in the treatment solution is a silicone-polyurethane copolymer.

27. A method for rendering a silicone catheter antiseptic, comprising:

- (i) placing the silicone catheter in an impregnating solution comprising (a) a solvent which causes the catheter to swell; (b) between 1 and 5 percent of chlorhexidine free base; (c) between 0.5 and 5 percent of triclosan; and (d) between 1 and 10 percent of a biomedical polymer, wherein the molar ratio of chlorhexidine free base to triclosan is between 1:1 and 1:3;
- (ii) soaking the catheter in the impregnating solution for a period of time sufficient to allow the catheter to swell and to incorporate chlorhexidine free base and triclosan;
- (iii) removing the catheter from the impregnating solution; and
- (iv) drying the catheter.

28. The method of claim 27, wherein the biomedical polymer is a biomedical silicone polymer.

29. The method of claim 27, further comprising the step of dipping the catheter, after drying according to step (4), into a second coating solution comprising a biomedical polymer.

30. The method according to claim 29, wherein the biomedical polymer in both the impregnating solution and the second coating solution is a biomedical silicone polymer.

31. A hydrophobic polymeric medical article which has been impregnated with a treatment solution comprising (i) between about 1 and 10 percent of a hydrophilic polymer; (ii) between 1 and 5 percent of chlorhexidine free base; and (iii) between 0.5 and 5 percent of triclosan, wherein the molar ratio of chlorhexidine free base to triclosan is between 1:1 and 1:3.

32. The medical article of claim 31 which is fabricated from a hydrophobic polymer selected from the group consisting of polytetrafluoroethylene, Dacron, polyvinylchloride, biomedical silicone polymer, and silicone polyurethane copolymer.

33. The medical article of claim 31 wherein the hydrophilic polymer is a biomedical polyurethane.

34. A method of preparing an infection resistant medical article comprising:

- (i) placing the medical article in an impregnating solution comprising (a) a solvent selected from the group consisting of water, reagent alcohol, tetrahydrofuran, and mixtures thereof; and (b) chlorhexidine free base and triclosan, in a molar ratio of between 1:1 and 1:3, wherein the total weight of chlorhexidine free base and triclosan is between 1 and 10 percent of the weight of the impregnating solution;
- (ii) soaking the medical article in the impregnating solution for a period of time sufficient to allow the medical article to swell and to incorporate chlorhexidine free base and triclosan;
- (iii) removing the medical article from the impregnating solution; and
- (iv) drying the medical article.

35. The method of claim 34, wherein the solvent in step (1)(a) is a mixture of reagent alcohol and tetrahydrofuran.

36. The method of claim 34, wherein the ratio of chlorhexidine free base and triclosan in step (1)(b) is about 1:2.

37. The method of claim 34, wherein the total weight percent of chlorhexidine free base and triclosan in step (1)(b) is about 2-10.

38. The method of claim 34, which has further been coated with a coating solution comprising a biomedical polymer.

39. The method of claim 38, wherein the biomedical polymer in the coating solution comprises an antimicrobial agent.

40. The method of claim 34 which is fabricated from polyurethane.

41. The method of claim 40 which is a polyurethane catheter.

42. The method of claim 41 in which both the external and internal surfaces of the catheter are brought into contact with the impregnating solution.

43. The method of claim 41 in which only the external surface of the catheter is brought into contact with the impregnating solution.

44. The method of claim 41, in which only the internal surface of the catheter is brought into contact with the impregnating solution.

45. A medical article which has been impregnated by a method comprising:

- (i) placing the medical article in an impregnating solution comprising (a) a solvent selected from the group consisting of water, reagent alcohol, tetrahydrofuran, and mixtures thereof; and (b) chlorhexidine free base and triclosan, in a molar ratio between 1:1 and 1:3, wherein the total weight of chlorhexidine free base and triclosan is between 1 and 10 percent of the weight of the impregnating solution;

- (ii) soaking the catheter in the impregnating solution for a period of time sufficient to allow the medical article to swell and to incorporate chlorhexidine free base and triclosan;

- (iii) removing the medical article from the impregnating solution; and

- (iv) drying the medical article.

46. The medical article of claim 45, wherein the solvent in step (1)(a) is a mixture of reagent alcohol and tetrahydrofuran.

47. The medical article of claim 45, wherein the ratio of chlorhexidine free base and triclosan in step (1)(b) is about 1:2.

48. The medical article of claim 45, wherein the total weight percent of chlorhexidine free base and triclosan in step (1)(b) is about 2-10.

49. The medical article of claim 45, which has further been coated with a coating solution comprising a biomedical polymer.

50. The medical article of claim 49, wherein the biomedical polymer in the coating solution comprises an antimicrobial agent.

51. The medical article of claim 45 which is fabricated from polyurethane.

52. The medical article of claim 51 which is a polyurethane catheter.

53. The medical article of claim 52 in which both the external and internal surfaces of the catheter are brought into contact with the impregnating solution.

54. The medical article of claim 52 in which only the external surface of the catheter is brought into contact with the impregnating solution.

55. The medical article of claim 52, in which only the internal surface of the catheter is brought into contact with the impregnating solution.

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